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REVIEW ARTICLE

Hepatosplenic T-cell lymphoma and inflammatory bowel disease

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KEYWORDSHepatosplenic T-cell lymphoma;
Lymphoma;
Infliximab;
6-Mercaptopurine;
Inflammatory bowel disease**Abstract**

Objective: This article reviews the current literature and knowledge about hepatosplenic T-cell lymphoma (HSTCL), providing an overview of the clinical features, a description of its pathology and immunophenotypic traits in relation to other lymphomas. In addition, we explore the history of reported cases of hepatosplenic T-cell lymphoma in relation to the possible existence of a causal relationship between infliximab use and HSTCL. The treatments for HSTCL will be briefly addressed.

Methods: A comprehensive literature search using multiple databases was performed. Keyword search phrases including "lymphoma," "hepatosplenic T-cell lymphoma," "Inflammatory bowel disease," "6-mercaptopurine," and "infliximab" were used in various combinations. In addition references from published papers were reviewed as well.

Results: There are over 200 reported cases of HSTCL. Only 22 cases of hepatosplenic T-cell lymphoma are associated with IBD treatment. Clinicians usually reserve immunomodulators and biologics for moderate to severe IBD cases. The ultimate goal of therapy is to control inflammation and therefore allow mucosal healing. IBD patients demonstrating mucosal healing are less likely to undergo surgery and experience complications related to their disease. We manipulate the immune system with corticosteroids, immunomodulators, and biologics, therefore causing bone marrow suppression. With bone marrow suppression, malignant degeneration may begin through selective uncontrolled cell proliferation, initiating HSTCL development in the genetically susceptible.

Conclusion: Hepatosplenic T-cell lymphoma is a rare disease, often with a poor outcome. With the increasing number of reported cases of HSTCL linked to the use of infliximab, adalimumab, and AZA/6-MP, there appears to be an undeniable association of HSTCL development with the use of these agents. This risk is unquantifiable. When considering the rarity of cases and the multiple complications with uncontrolled disease, however, the benefit of treatment far outweighs the risk.

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1. Introduction

For the last decade, hepatosplenic T-cell lymphoma (HSTCL) was a relatively unknown disease. In fact, although it was in 1981 that Kadin and colleagues first recognized it as a distinct entity from other peripheral T-cell lymphomas, the medical world did not quite catch on to the significance of what HSTCL entails.¹ With the tantalizing hope of control and of relief for patients suffering from inflammatory bowel disease (IBD) with immunomodulating and biological agents, the rare disease of HSTCL began to gain worldwide recognition. There are studies that suggest an increased malignancy and lymphoma risk in patients with IBD.^{2–4} But perhaps, a more specific question would be whether lymphoma, including HSTCL, displays a higher incidence in IBD patients who received immunomodulating agents and/or biological agents. If so, are clinicians putting their IBD patients at increased risk for HSTCL with the use of these medications?

Between the years 2001 and 2005, 70,214 new cases of non-Hodgkin's lymphoma (NHL) were diagnosed. In the general population, the incidence of NHL is 17.2 per 100,000 individuals per year. Non-Hodgkin's lymphoma is usually a diagnosis of the older population, with a peak in the 6th to 7th decade. The incidence of extranodal NHL is 5.0 per 100,000.⁵ In the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Database, there are a total of 34 reported cases between 1973 and 2005 of HSTCL, a subtype of extranodal NHL. This equates to an incidence of only 0.046 per 100,000 individuals or 1 case per 1088 patient years. Among the 34 cases, 24 were men, and 10 were women. The age breakdown is as follows: 4 patients were less than the age of 19, 6 patients were in their 20s, 12 patients were in their 30s, 5 patients in their 40s, 2 patients in their 50s, and 5 patients older than 60 years old.⁵

Hepatosplenic T-cell lymphoma is a rare and aggressive extranodal form of non-Hodgkin's lymphoma that affects predominantly men. In addition to hepatosplenic involvement as its name suggests, HSTCL is also characterized by a lack of lymphadenopathy, the presence of cytopenias, and sinusoidal infiltration of the splenic red pulp, liver, and bone marrow.^{6–8} HSTCL has a rapidly progressive course. The mean time of diagnosis to death is less than 16 months.^{8–10} Since Farcet et al. proposed HSTCL as a separate entity from other peripheral T-cell lymphomas, there has been approximately 238 cases of HSTCL reported worldwide through literature search.^{7,8,10–102}

Among the medical community, especially the pediatricians, there is a growing concern that HSTCL is an emerging disease of the young, especially of pediatric patients treated with biologic agents. This fear may not be warranted. Of all the reported cases (not including the SEER Database), only 25 cases of hepatosplenic T-cell lymphoma are associated with IBD treatment. An overwhelming 73% of HSTCL were de novo. The de novo group includes patients that were explicitly stated as healthy, which entails lack of autoimmune diseases, treatment with immunosuppressants, history of transplant, or any other primary malignancies. Characteristics of patients who developed HSTCL de novo, including mean age, sex prevalence, presentation, histopathology, and prognosis did not differ from the patients with some degree of immunosuppression.^{10,16,17,20} The second largest incidence (18%) is found in immunocompromised patients. This group consists of patients with renal and heart transplant, chronic steroid use, systemic lupus erythematosus, recurrent malarial infections, sickle cell anemia, dermatomyositis, autoimmune hepatitis, and primary malignancies such as Hodgkin's lymphoma, acute myelogenous leukemia, and multiple myeloma. The third largest group of HSTCL (10%) was found in IBD patients exposed to treatment with immunomodulators and/or biologics (Fig. 1).

Other inflammatory and autoimmune diseases such as peripheral and axial arthritis, Sjogren's disease, polymyositis, systemic sclerosis, dermatitis herpetiformis associated with celiac disease, psoriasis, Hashimoto's thyroiditis have not been linked to the development of HSTCL. But these diseases have all been shown to have a higher risk of developing non-Hodgkin's lymphoma compared to the general population.¹⁰³

The lack of association with HSTCL in these inflammatory diseases may be explained by the fact that B lymphocytes, not gamma-delta T cells, play a predominant role in immunity in the periphery and joint space. The chronic inflammation may be a factor in precipitating the malignant degeneration of the B cells involved. Some studies suggest a 100-fold risk with developing diffuse large B-cell lymphoma in individuals with the highest rheumatoid arthritis disease severity when compared to patients with low global disease activity.¹⁰³ Sjogren's disease, systemic lupus erythematosus, and celiac disease are also associated with large B-cell lymphoma development.¹⁰³ The specific associations with each specific inflammatory disease have been reviewed elsewhere.¹⁰³

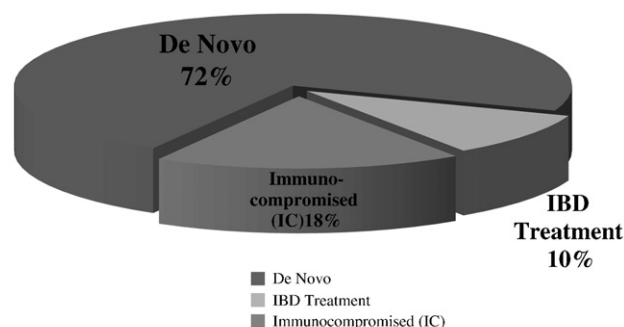


Figure 1 Distribution of HSTCL cases.

2. Clinical presentation

HSTCL affects predominantly adult men, with a median age of 35 years, with an age range of 8 months to 68 years.^{8,10,23} Patients typically present with splenomegaly (96%), hepatomegaly (77%), systemic B-type symptoms (high fevers, night sweats, and weight loss) (70%), bone marrow involvement (72%), and thrombocytopenia (89%).^{8,10,16} Even in patients who have undergone a splenectomy, the severity of thrombocytopenia increases with disease progression. Other common presenting signs include concomitant anemia or leukopenia with thrombocytopenia, elevated lactate dehydrogenase (LDH), elevated liver enzymes, and symptoms of hepatitis.^{8,13,104} Atypical findings include lymphocytosis, peripheral blood infiltration by tumor cells, and simultaneous involvement of other organs (Table 1).¹⁰⁵

3. Pathology

A majority of reported cases of HSTCL are of the gamma–delta T-cell receptor subtype. Case reports of the alpha–beta subtype have been described as well. The alpha–beta subtype of HSTCL demonstrates a predominance in women, but is very similar to the gamma–delta subtype in clinical presentation, pathology, and cytogenetics.^{9,17} It is consid-

ered a subvariant of HSTCL according to the World Health Organization (WHO) classification of lymphomas.^{9,10}

T cells are vital to the proper function of cell-mediated immunity. Specifically, gamma–delta T cells are a population of T cells comprising 5% of the adult T-cell population that are important to mucosal immunity. Gamma–delta T cells display an affinity for the epithelial layer of the intestines, skin, and red pulp of the spleen.^{106,107} A knockout mice study involving $\gamma\delta$ T cells, confirm the immunoregulatory role of $\gamma\delta$ T cells at the intestinal epithelium.¹⁰⁸ Furthermore, Nanno et al. suggest that $\gamma\delta$ T cells are the key for proinflammation in colitis. In the $\gamma\delta$ T-cell knockout mice group, less severe colitis, a reduction in the production of proinflammatory proteins, and a decrease of neutrophilic infiltration, were observed.¹⁰⁸

Like other peripheral T-cell lymphomas, HSTCL may demonstrate erythrophagocytosis.^{1,9} Erythrophagocytosis by reactive tumor cells have been reported rarely.^{9,10,81} Pathological features include a significantly enlarged spleen, with global infiltration of the splenic red pulp with atypical lymphocytes.¹⁶ In the liver, there is a sinusoidal distribution of tumor cells that may be accompanied by periportal and portal invasion.^{8,105} The involved bone marrow is hypercellular, and may include plasmacytosis and blood vessel malformation.¹⁰⁵ However, bone marrow infiltration is often subtle and requires specific immunohistochemical staining for T-cell antigens.^{105,109} Tumor cells are homogeneous and usually intermediate in size, but cells can vary in size with each respective case. The bone marrow infiltration pattern changes with disease progression, favoring an interstitial spread over the characteristic sinusoidal pattern, and tumor cells transform into larger cells, resembling blasts.^{105,109}

4. Immunophenotypic traits

Cytometric immunophenotyping plays a central role in confirming the diagnosis of HSTCL. Immunophenotyping has been reviewed in detail.^{9,10,16,109} In contrast to the mucosal and cutaneous gamma–delta T-cell lymphomas, hepatosplenic T-cell lymphoma consists of atypical lymphocytes that are cytotoxically inactive.^{6,16,109} This is exemplified by neoplastic cells staining positive for T-cell restricted intracellular antigen (TIA-1), and negative for granzyme B and perforin (proteins released by cytotoxic T cells).^{16,109} The most common immunophenotype of HSTCL is listed in Table 2. In order to differentiate between the gamma–delta and alpha–beta T-cell receptor (TCR) chains, monoclonal antibodies specific to each chain are used.¹⁰ With other non-hepatosplenic gamma–delta T-cell lymphomas, there is a strong association with Epstein-Barr virus (EBV).¹¹⁰ Interestingly, the presence of EBV infection in tumor cells of HSTCL patients, detected by in situ hybridization for EBV- encoded small RNA (EBER), is extremely atypical and therefore rarely seen.^{9,10,15,18,84}

Cytogenetic analysis reveals the abnormality isochromosome 7q to be present consistently in all atypical lymphoid cells of HSTCL.^{86,97,109} There have been recent reports of ring chromosome 7, a clonal aberration of 7q, in HSTCL patients.^{25,47} Both chromosomal abnormalities lead to an amplification of the long arm of Chromosome 7 therefore the amplification of oncogenes, and varying degrees of 7p deletion, the location of

Table 1 Clinical presentation (symptoms, laboratory findings).

	% Patients with involvement
<i>Symptoms</i>	
Splenomegaly	97
Hepatomegaly	78
Systemic B symptoms	70
Lymphadenopathy	Approximately 0
<i>Lab findings</i>	
Bone marrow involvement	73
Thrombocytopenia	90
Anemia	85
Leukopenia	72
Elevated LDH	60
Elevated liver enzymes	46

Table 2 Most common immunophenotypic traits.

	Positive (+)/negative (–)
Cytolytic granule proteins	
TIA-1	+
Granzyme B	–
Perforin	–
Natural killer cell associated	
CD16	+/-
CD56	+
CD57	–
T cell associated	
CD2	+
CD3	+
CD4	–
CD5	–
CD7	+/-
CD8	–
CD16	+/-
CD25	–
CD30	–
CD38	+
Epstein-Barr virus	–

tumor suppressor genes.⁶⁹ Other defects include trisomy 8 and loss of the Y chromosome.^{10,86,91,97}

5. Treatment of HSTCL

Hepatosplenic T-cell lymphoma is a rapidly progression disease with a mean survival of less than 16 months, regardless of the treatment modality. Multiple treatment modalities have been used, including cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), CHOP-like therapies, interferon alpha therapy, splenectomy, platinum based chemotherapy, and allogeneic or autologous bone marrow or stem cell transplantation. None are curative and rarely is complete remission accomplished and sustained.^{7,8,10} Individual case reports on HSTCL treatment seem promising. Jaeger and colleagues recently documented complete remission in a HSTCL patient with Rituximab with CHOP, followed by a combination of alemtuzumab and cladribine for a total of 27 months.²⁹ Rituximab selectively binds to CD20, a marker for both malignant and normal B cells. In the patient mentioned above, the immunophenotypic trait included being CD20 positive.²⁹ This example serves to emphasize that HSTCL's immunophenotype may vary from patient to patient. Therefore it may be beneficial to tailor treatment to each individual case according to immunophenotypic traits.

6. HSTCL and IBD treatment

Immunosuppression with corticosteroids, cyclosporine, infliximab, adalimumab, azathioprine, and 6-mercaptopurine have been associated with HSTCL.^{10,13,14,32,111} In addition, many HSTCL cases are linked to alterations or deficits in the immune system exemplified by cases in severe immunodeficiency disorders, multiple recurrent malarial infections,

and pregnancy.^{21,23,24} There is an obvious association between immunosuppression and the development of HSTCL. By manipulating the immune response of IBD patients with medications, there may be an increased chance of developing HSTCL.

The efficacy of corticosteroids and thiopurine therapy with azathioprine and 6-mercaptopurine in IBD has been well established. But there are risks that come with using these medications. One major concern is the increased incidence of lymphoma. A meta-analysis performed by Kandiel and colleagues suggests that the risk of lymphoma in IBD patients treated with AZA or 6-MP is four times the risk of the general population.¹¹² However, a confounding factor to the study may include the severity of the disease in relation to the population of IBD patients who actually receive immunomodulating treatment. Preliminary results from a French cohort study involving 20,802 IBD patients suggest an increased risk for development of lymphoma especially with AZA use.¹¹³ Disanti et al. performed a study that examined the lymphoma incidence in IBD patients with 6-MP induced sustained leukopenia. Their findings indicate that patients on 6-MP treatment that developed sustained leukopenia, defined as leukocyte count of less than or equal to 4000 for a total of ≥ 20 days, had a statistically significant higher incidence of lymphoma (7%) even after confounding factors were accounted for.¹¹⁴ The exact cause of this leukopenia leaves room for discussion. It is unlikely that the sustained leukopenia is a result of overdosing. The observed leukopenia is likely the result of the unmasking of a preleukemic state already present in the host's bone marrow.

Early studies suggest that 6-MP and thioguanine metabolites cause immunosuppression and cytotoxicity by inhibiting purine synthesis through direct binding to guanine triphosphate. However, Tiede and colleagues propose that the mechanism of action is through the inhibition of Ras-related C3 botulinum toxin substrate 1a (Rac1), a GTP-binding protein.¹¹⁵ They demonstrate that the 6-MP metabolite, 6-thioguanine triphosphate binds to Rac1 directly. Even at low concentrations of AZA, Rac1 inhibition along with costimulation of CD28 leads to apoptosis.¹¹⁵ 6-thioguanine nucleotide (6-TGN) levels closely correlate with therapeutic efficacy and myelotoxicity.¹¹⁶ Approximately 5% of patients treated with AZA or 6-MP may not develop apoptosis, and are considered drug failures and possibly have a phosphorylation defect.

Immunomodulator use is usually reserved for moderate to severe disease. Clinicians generally utilize a milligram per kilogram approach or a dosage regimen tailored through monitoring 6-MP metabolites. Most clinicians traditionally start at low doses and slowly titrate up the administered dosage according complete blood counts, closely monitoring for myelotoxicity and adverse reactions.

Pharmacogenomic studies of thiopurine metabolism reveal a metabolite range from 230 to 400 for optimal therapeutic benefit.¹¹⁶ In theory, if the magnitude of 6 TG binding to nucleotides is important for oncogenesis then traditional dosing at milligram per kilograms (mg/kg) and observing for leukopenia may expose the patient to more risk.

Accomplishing the desired therapeutic response, while protecting the patient's safety, may prove to be difficult. Given the narrow therapeutic index balanced with the

pharmacokinetic variability determined by genetics, it may be safer to individualize, and therefore optimize therapy according to TPMT genotyping and metabolite levels.^{116,117} The genotype profiles and recommendations for metabolite level monitoring have been reviewed in detail elsewhere.¹¹⁶

Multiple studies, such as the ACCENT trials and ACT trials, demonstrated infliximab to be beneficial in controlling active mucosal inflammation and in maintaining remission in IBD.^{118–120} There is conflicting evidence for the association of infliximab use and increased risk for lymphoma. When Wolfe and colleagues performed a study including 18,572 patients with rheumatoid arthritis, a causal relationship between infliximab use and development of lymphoma could not be established.¹²¹ In a multicenter-matched study, Biancone and colleagues revealed that there is no data supportive of a causal relationship between infliximab use and development of malignancy.¹²² Only nine out of 404 patients treated with infliximab developed cancer, including 3 cases of breast adenocarcinoma, 1 laryngeal carcinoma, 1 basal cell carcinoma, 1 cholangiocarcinoma, 2 cases of rectal carcinoma, and 1 case of leukemia. The incidence of malignancy was comparable to the control group that had 7 cases of malignancy out of 404 patients.¹²² A meta-analysis of anti-TNF therapy in patients with rheumatoid arthritis (RA) which included nine randomized control trials, suggested an increased risk of malignancy with anti-TNF therapy that was dose dependent.¹²³ The majority of the patients developed malignancy early during treatment, with 19/34 patients diagnosed with new malignancy within 20 weeks of starting treatment. This suggests that a number of these newly diagnosed malignancies may represent preexisting cancers. This study also contradicts findings from a Swedish population based study which concluded that there was no increased risk of solid malignancies in patients treated with anti-TNF therapy with RA compared to other RA patients.¹²⁴

Of note, there have been a total of 19 cases of HSTCL linked to infliximab use and 4 cases linked to the use of adalimumab (Table 3).¹¹¹ Of the 19 infliximab cases, only 4 cases involved patients ≤ 18 years old. Along with exposure to biologics, each patient received either AZA, 6-MP, or prednisone at some point during their respective treatment course. There are 6 reported cases of HSTCL in patients who had no prior exposure to biologics, (3 cases with AZA, sulfasalazine and/or prednisone, 1 case with AZA monotherapy, 1 case with AZA and unknown IBD therapy, 1 case with 6-MP exposure).^{16,19,22,125,126} As mentioned previously there could be many factors playing into the development of HSTCL in IBD patients treated with biological agents. It appears that factors including severity of IBD in patients who ultimately receive biologic therapy, the possibility of dose-related effect, the differences in each patient's innate immune response and therefore varying degrees of immunosuppression accomplished by biologics, may singularly or collectively contribute to HSTCL development. Perhaps, a synergistic or catalytic effect of dual therapy with immunomodulators and biological agents propels a malignant degeneration and thus the development of HSTCL.

If one decides to incorporate biologics and immunomodulating therapy, the risk of inducing HSTCL is there. How should clinicians approach IBD patients in relation to treatment with immunomodulators, anti-TNF therapy, or a combination of both? There is a clear benefit to treating IBD

patients with immunomodulators and anti-TNF therapy to control disease progression. Lewis and colleagues demonstrated an increased quality-adjusted life expectancy, measured by the Crohn's Disease Activity Index (CDAI), in Crohn's patients using azathioprine to maintain disease remission.¹²⁷ Although there have been case reports of patients developing HSTCL after being treated with immunomodulating and biological agents, it is still relatively rare.

Recent preliminary results from the Study of Biologic and Immunomodulator Naïve Patients In Crohn's Disease (SONIC) trial, give tangible hope to controlling inflammatory bowel disease with both immunomodulators and biologics.¹²⁸ IBD patients treated with both AZA and infliximab demonstrated an overwhelming response with 56.8% maintaining corticosteroid-free clinical remission at Week 26. More significantly, at 26 weeks a large proportion of patients on dual therapy displayed mucosal healing.¹²⁸ The presence of mucosal healing signifies a significant decrease in active inflammation and successful regeneration of normal mucosa.¹²⁹ Mucosal healing is a favorable prognostic indicator of disease activity. IBD patients demonstrating mucosal healing are less likely to undergo surgery and experience complications related to their disease.^{130,131} More long-term studies need to be done in order to further determine if there is a causal relationship with biologics and HSTCL.

Delineating the exact mechanisms for malignant degeneration is important for understanding the observed link between IBD and HSTCL. It is well known that chemicals, medications, viruses, radiation, and rapid cell turnover initiate neoplastic transformation. A disruption in the cell cycle check points either through alterations in tumor suppressor genes and proto-oncogenes, or the DNA sequence itself, changes cell signal transduction. Patients with IBD experience chronically active inflammation, initiating constant cell regeneration and rapid turnover. Treatment with immunomodulators and biologics may be the epigenetic factor that allows selective uncontrolled cell proliferation and therefore initiate HSTCL development in the genetically susceptible. But why is HSTCL so rapidly progressive? It could be that a latent viral infection had the opportunity to permanently alter the RNA/DNA sequence previously. The immunosuppressing agents could be the jump start needed to complete the process. Continued research in this area may lead to the answer, as the exact mechanisms remain unknown.

When formulating an IBD treatment plan, factors to consider in each patient's case include the severity of patient's disease, history of intolerable side effects from specific agents, history of failure of specific therapy, and the patient's decision after knowing the benefits and reported risks of each class of drugs.^{132–134}

7. IBD treatment strategies

The third largest group of patients with HSTCL was found in IBD patients exposed to treatment with immunomodulators and/or biologics. This makes up only 10% of all reported cases. Regardless of the rarity of these cases, the increased risk of HSTCL development is present. This risk further complicates the clinical management of patients with moderate to severe inflammatory bowel disease, especially

Table 3 Cases of HSTCL associated with IBD treatment.

Therapy exposure						
Case #/reference	Age/sex	IBD Dx	HSTCL subtype	A AZA/6-MP	Infliximab and AZA/6-MP	Other Tx
1 ¹⁶	?	UC	– γ/δ	AZA 17 yrs		?
2 ²²	35 M	CD	– γ/δ , Isochromosome 7q, Trisomy 8	AZA 5.6 yrs		– Sulfasalazine – Steroid for 10 yrs
3 ¹⁹	18 M	CD	– γ/δ	AZA 6 yrs		?
4 ¹²⁶	?	CD	Unknown	AZA 4 yrs		– Prednisone – IV Cyclosporine
5 ¹¹	30s M	CD	– γ/δ	6-MP		
6 ¹²⁵	15 M	UC	Unknown	AZA 9 yrs		– Sulfasalazine – Prednisone
7 ¹³	17 F	CD	– α/β		6-MP 4.5 yrs Infliximab: 20 doses of 5 mg/kg	– Prednisone – Mesalamine
8 ¹³⁵	31 M	CD	– γ/δ , Isochromosome 7q	6-MP 5 yrs Infliximab: 3 doses of 300 mg		– Mesalamine – Prednisone
9 ¹¹¹	19 M	CD	– γ/δ	AZA 7 yrs Infliximab: 3 doses of 300 mg/kg		None
10 ¹¹¹	18 M	CD	– γ/δ , Isochromosome 7q	AZA 5 yrs, 6-MP Infliximab: 5 doses of 5 mg/kg		– Prednisone, budesonide
11 ¹¹¹	19 M	CD	– α/β	AZA 6 yrs, 6-MP Infliximab: 14 doses of 550–600 mg		– Mesalamine – Prednisone
12 ¹¹¹	12 M	CD	– γ/δ , Isochromosome 7q	AZA 4 yrs, 6-MP Infliximab: 21 doses of 300 mg		– Mesalamine
13 ¹¹¹	15 M	CD	– γ/δ , Isochromosome 7q	AZA 2.5 yrs Infliximab: 13 doses of 150–200 mg		– Mesalamine – Prednisone
14 ¹¹¹	31 M	CD	– γ/δ	6-MP 3 yrs Infliximab: 1 dose of 5 mg/kg		– Mesalamine – Prednisone – MTX
15 ¹¹¹	22 M	CD	– α/β , Trisomy 13	6-MP 4 yrs Infliximab: 24 doses of 5 mg/kg		– Mesalamine, Basalazide – Prednisone
16 ¹¹¹	22 M	IC	– γ/δ	AZA 5 yrs Infliximab: 1 dose of 5 mg/kg		– Mesalamine – Steroids
17 ¹¹¹	31 M	CD	– α/β , Trisomy 8, loss of chromosome y, 7p deletion	AZA 5 yrs Infliximab: 3 doses of 5 mg/kg		– Sulfasalazine – Prednisolone
18 ¹¹¹	40 M	CD	– γ/δ	AZA 7 yrs Infliximab: 3 doses of 5 mg/kg		– Prednisone
19 ¹¹¹	21 M	UC	Unknown	6-MP 7 yrs Infliximab: ? doses of 5 mg/kg		– Mesalamine – Adalimumab
20 ¹¹¹	19 M	CD	Unknown, Isochromosome 7q	6-MP Infliximab: 18 doses of 5–10 mg/kg		– Mesalamine – Prednisone
21 ¹¹¹	29 M	CD	– γ/δ	AZA 11 yrs Infliximab: 3 doses of 400 mg		– Adalimumab
22 ¹¹¹	58 M	CD	Unknown	–AZA, unknown duration –NO infliximab history		– Adalimumab

CD, Crohn's disease; UC, ulcerative colitis; IC, indeterminate colitis; Dx, diagnosis; yrs, years.

in the pediatric population. The current clinical opinion is that there is an increased risk of HSTCL development associated with the use of immunomodulators and biologic agents. However, the good news is approximately one million patients have received this medication over time and throughout that time interval, a progressive increase in HSTCL has not been observed. When the first cases of HSTCL associated with immunomodulator use were reported, most

pediatricians immediately stopped using 6-MP, and implemented infliximab monotherapy. In the survey conducted by Cucchiara et al. for the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), 97% of pediatric patients with Crohn's Disease were treated with immunomodulators and infliximab before the year of 2007. This number significantly dropped when case reports revealed Crohn's patients on combined immunomodulator

and infliximab therapy may have an increased risk of developing HSTCL. Among the clinicians surveyed, only one third of the pediatricians were still using thiopurines. Most changed their management to include either monotherapy with infliximab, or combined therapy with methotrexate and infliximab.¹³⁶ Pediatricians at our institution are starting to use 6-MP with infliximab again.

An important question, without a clear guideline established on objective data, remains. What is the best approach in utilizing immunomodulators and biologics that would guarantee optimal patient outcomes? There are multiple treatment algorithms available in regards to the treatment of moderate to severe IBD. The plan of treatment often reflects philosophical differences depending on the institution one trained in or practices in. More importantly, an individual physician's treatment goals or end points, whether it be symptomatic control and/or mucosal healing, prevention of immunogenicity, or increasing the therapeutic response to biologic therapy, often dictate the treatment plan. Treatment strategies include monotherapy with biologics or immunomodulators, the use of immunomodulators in concomitant therapy or in bridging therapy, and early aggressive therapy with both agents (the "top-down approach"). There is clinical evidence that support and challenge the methods listed above.

The use of immunomodulators and corticosteroids represent the traditional approach before the introduction of biologics. The disadvantage of this approach evolved around the effects of corticosteroids. However, the most recent SONIC trial reveals that a small percentage of patients will respond with immunomodulator therapy with modest mucosal healing.¹²⁸ This category of therapy in this study provides a reference point to compare various treatment strategies in terms of response and mucosal healing.

Results from a multi-center randomized control trial, suggest that monotherapy with infliximab was just as effective in controlling disease, as measured by mucosal healing and clinical scores (Crohn's Disease Activity Index [CDAI] and Inflammatory Bowel Diseases Questionnaire [IBDQ]), as was concomitant therapy with immunosuppressives and infliximab.¹³⁷ However, Van Assche et al., also discovered that patients on monotherapy had lower infliximab trough levels, corresponding to higher C-reactive protein levels and higher clinical scores. In addition, it appears that over time, patients on monotherapy developed immunogenicity, as indicated by the increase in patients requiring adjustments to dosing schedules, the development of intolerance, and the loss of response.¹³⁷ If the treatment goal is to effectively inhibit immunogenicity, then concomitant therapy with immunomodulators may be the answer. Concomitant therapy inhibits the formation of antibodies to infliximab (ATIs), resulting in higher infliximab trough levels and therefore an improved therapeutic response.^{128,138–140}

Bridging therapy or induction of clinical remission with infliximab followed by maintenance with immunomodulators alone, has advantages. A two year open-label randomized control trial in Belgium compared the effectiveness of bridging therapy with the conventional treatment regimen, which included sequential addition of corticosteroids, azathioprine, and infliximab.¹⁴¹ All 133 Crohn's patients were naïve to treatment with steroids, immunosuppressing agents (methotrexate or azathioprine), and biologic agents.

This study proved that bridging therapy was superior to the conventional "step-up" therapy. Sixty percent of patients who received early combined therapy with 3 infusions of infliximab with azathioprine, who were then maintained on azathioprine alone, demonstrated clinical remission at 26 and 52 weeks. This significant level of remission is in contrast to 35.9% and 42.2% of the patients who were randomized to conventional therapy, at 26 and 52 weeks respectively. In addition they found that patients who were bridged to immunosuppressive therapy, had a significant rapid reduction in C-reactive protein levels by week 10, as well as more ulcer free patients (73.1%) at week 104.¹⁴¹ Further investigations on bridging therapy are of interest, as there is a concern of the cost effectiveness of the use of biological agents.

Early aggressive therapy is supported by multiple studies. The SONIC trial makes a strong argument for the benefits of concomitant therapy and early aggressive therapy in Crohn's disease.¹²⁸ Early aggressive therapy with infliximab and azathioprine maintained corticosteroid-free clinical remission and resulted in the best mucosal healing.¹²⁸ Most data on the use of early aggressive therapy in inflammatory disease processes can be found in large randomized prospective rheumatoid arthritis trials. There are multiple randomized control trials involving the concomitant use of anti-TNF inhibitors with immunomodulators compared to monotherapy that demonstrate an enhanced clinical response with greater improvements in functionality and quality of life, as well as prevention of the progression of joint destruction or erosions.^{142–148} A recent study performed by Emery et al. found that combination therapy with golimumab and methotrexate in methotrexate and anti-TNF naïve patients, was more efficacious than monotherapy with either methotrexate or adalimumab, in achieving better clinical response rates.¹⁴⁸

The best control of immunogenicity was with oral methotrexate and remicade in the initial RA trial with a resultant 8%.¹⁴⁹ Additionally, the immunogenicity was very low with concomitant therapy in the SONIC trial of 0.9%.¹²⁸ HSTCL has not been reported with the use of methotrexate. However, oral methotrexate therapy has not been proven to work with Crohn's disease. The incidence of immunogenicity with sporadic therapy was 30% in the 54 week Crohn's disease trial.¹¹⁹

Early aggressive therapy in RA altered the natural history of the disease. This change is easier to demonstrate in RA compared to CD secondary to scoring systems and objective measurements of disease progression, i.e. joint destruction. Bridging therapy and early aggressive therapy in CD suggests that these therapies may change the natural history of this disease. Multi-center randomized trials will be needed to further define the evolving philosophical approaches and end points for therapy.

8. Conclusion

Hepatosplenic T-cell lymphoma is a rare disease, often with a poor outcome. With the increasing number of reported cases of HSTCL linked to the use of infliximab, adalimumab, and AZA/6-MP, there appears to be an undeniable association of HSTCL development with the use of these agents. But

unfortunately, this risk is not quantifiable. But with its presence, both patients and clinicians may need to think twice about controlling IBD with these agents. When considering the rarity of cases and the multiple complications with uncontrolled disease, however, the benefit of treatment far outweighs the risk. A more prudent approach to the treatment and management of IBD patients, may just be to stick to the fundamentals of the practice of medicine: combine clinical experience, established evidence based guidelines, and meticulous consideration into each individual patient's case.

Conflicts of interest statement

We have not published or submitted any similar or related studies. No conflicts of interest exist.

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AT participated in the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis. PT conceived of the study, and was involved in the critical revision of the manuscript for important intellectual content and statistical analysis. All authors read and approved the final manuscript.

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